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Review of mortality from the STRIDER UK trial of sildenafil therapy for the treatment of severe early-onset fetal growth restriction

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Severe early-onset fetal growth restriction (FGR) is an untreatable condition associated with significant mortality and morbidity for the fetus and neonate. There has been growing interest in novel therapies such as nitric oxide donors/promoters to improve placental function and outcomes for these high-risk pregnancies. The recently published STRIDER UK trial was designed to test the effectiveness of sildenafil (25mg three times a day) versus placebo at prolonging gestation in severe early-onset FGR [1].

The STRIDER trials are a series of international randomised controlled studies with the goal of assessing the ability of sildenafil to improve pregnancy outcome in FGR. Five studies were initially planned (UK, New Zealand/Australia, Netherlands, Republic of Ireland and Canada), each with slightly different eligibility criteria and protocols. However, all studies agreed to use a centralised data management system to facilitate a pre-planned individual patient data meta-analysis based on an agreed protocol [2].

The STRIDER UK trial was the first to be completed and showed no beneficial effect of sildenafil on any outcome but also no significant difference in harm when compared to placebo. The trial reaffirmed that this is a very high-risk cohort with fetal demise occurring in 31% of pregnancies (21/70 sildenafil, 22/65 placebo) with a further 18% of infants suffering a neonatal death (10/49 sildenafil and 7/43 placebo).

Subsequently, the New Zealand/Australia trial was completed and showed similar results (unpublished). More recently the Dutch STRIDER trial was halted after 183 women were recruited; this was in response to concerns about a higher than expected neonatal mortality (19/71 sildenafil vs 9/63 placebo) and high rates of persistent pulmonary hypertension of the newborn (PPHN) in the sildenafil arm (17/64 sildenafil vs 3/58 placebo). In addition, there were concerns about likely futility in terms of being able to demonstrate an improvement in the primary outcome. Naturally, these findings raised significant concerns globally [3, 4].

The excess neonatal mortality of the Dutch trial, although not statistically significant, is a cause for concern, particularly as the data look consistent across the three trials (Figure 1). This will be further explored in the forthcoming IPD meta-analysis [2]

In light of these concerns, we have reviewed the STRIDER UK trial mortality and pathology data and present it here in order to complement the data already in the public domain (Table 1).

Unfortunately, post mortem and placental histology data are not available for all fetal and neonatal deaths. Three cases of fetal death (1 sildenafil and 2 placebo) have been excluded as these pregnancies were terminated due to severe early-onset FGR or related maternal conditions (HELLP syndrome).

There was a slight increase in time on sildenafil treatment for women with a fetal death compared to those on placebo, but the relevance of this difference is at present uncertain. Gestation and birthweight of stillborn infants were similar in the two groups. Most neonatal deaths occurred after the first week of life. Almost universally, post-mortem examinations showed features of chronic hypoxia only. Only two cases (one sildenafil and one placebo) were reported as being complicated by PPHN.

Nearly all placental pathology findings showed a spectrum of vascular under perfusion, characterised by maladapted maternal vessels, fibrin deposition, syncytial knotting, villous hypoplasia or

infarctions. We observed an incidence of chronic histiocytic intervillitis (CHI) of 15%, which is similar to the 16% reported in a similar population by Kingdom et al. [5].

In conclusion, we observed no obvious differences in clinically relevant pathological or histological findings between sildenafil or placebo arms of the STRIDER UK trial in pregnancies complicated either by fetal or neonatal death. The histological and post-mortem findings were in keeping with placental disease and chronic fetal hypoxia.

Whilst there appears to be no benefit from the use of sildenafil in pregnancies complicated by severe early-onset FGR, the possibility of excess neonatal mortality and the possible reasons for this warrant further study. We anticipate that our planned IPD meta-analysis [2] will provide further important insights in this area.

Table 1

a. FETAL DEATHS

	Sildenafil n=20	Placebo n=20
Gestational Age at IUD		
< 24 weeks	1 (5%)	2 (10%)
24 - 28 weeks	18 (90%)	17 (85%)
≥ 29 weeks	1 (5%)	1 (5%)
Birthweight		
< 500g	14 (70%)	18 (90%)
Time on Treatment		
≥ 7 days	19 (95%)	13 (65%)
IUD whilst on Treatment	17 (85%)	15 (75%)
Histological Features (non-exclusive)	n=17	n=11
• Chronic Histiocytic Intervillitis (CHI)	4 (24%)	0
• Placental underperfusion (infarcts, villous hypoplasia, fibrin etc.)	13 (76%)	11 (100%)
• Chorioamnionitis	1 (6%)	0
Post Mortem Features	n=5	n=5
• Chronic ischaemic changes (adrenal lipid, hypoxic neurons, thymic depletion etc.)	5 (100%)	4 (80%)
• Other	0	1 (20%)

b. NEONATAL DEATH

	Sildenafil	Placebo
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	n=10	n=7
Gestational Age at Birth		
< 26 weeks	2 (20%)	0
≥ 26 weeks	8 (80%)	7 (100%)
Birthweight		
< 500g	1 (10%)	3 (43%)
≥ 500g	9 (90%)	4 (57%)
Age at Death		
≥ 7 days	7 (70%)	4 (57%)
On Treatment at Decision to Deliver	9 (90%)	5 (71%)
Histological Features (non-exclusive)	n=3	n=3
• Chronic Histiocytic Intervillositis (CHI)	0	1 (33%)
• Placental underperfusion (infarcts, villous hypoplasia, fibrin etc.)	3 (100%)	2 (66%)
• Chorioamnionitis	0	0
Post Mortem Features	n=0	n=2
• Chronic ischaemic changes (adrenal lipid, hypoxic neurons, thymic depletion etc.)	0	1 (50%)
• Other	0	1 (50%)
Evidence of Pulmonary Hypertension	1	1

Figure 1

Forest Plot of publicly presented data on neonatal deaths from the three completed STRIDER trials (UK, New Zealand/Australia and Netherlands).

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